

Departement für Pferde  
der Vetsuisse-Fakultät Universität Zürich

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Arbeit unter wissenschaftlicher Betreuung von  
Dr. BVSc, DVCS, DVM, PhD, Dip ACVIM (LAIM) Katharyn J. Mitchell

**Diagnostic Value of Noninvasive Pulse Pressure Measurements in Warmblood  
Horses with Aortic Regurgitation**

**Inaugural-Dissertation**

zur Erlangung der Doktorwürde der  
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

**Julia Bögli**

Tierärztin von Seeberg, BE

genehmigt auf Antrag von

Prof. Dr. med. vet. PhD, Dipl. ACVIM/ECEIM Colin C. Schwarzwald, Referent

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### Diagnostic Value of Noninvasive Pulse Pressure Measurements in Warmblood Horses with Aortic Regurgitation

Noninvasive blood pressure (NIBP) and pulse pressure (PP) have not been reported in horses with aortic (AR) and mitral regurgitation (MR). This retrospective study describes NIBP and PP in healthy Warmblood horses and horses with AR and MR and suggests PP cutoffs to identify and stage AR severity. Standardized cardiovascular examinations, including NIBP and echocardiograms, of 73 horses (healthy, 10; AR, 31; MR, 32) were recorded. Cases were grouped based on regurgitation severity. Among healthy, MR, and AR groups and among AR severity groups, PP was compared and cutoffs determined by receiver operating characteristic curve analyses. Horses with AR had higher PP than those with MR (mean difference [95% confidence interval (CI)], +17 [9-26] mmHg,  $P < .001$ ) and controls (+17 [5-30] mmHg;  $P = .004$ ). Horses with severe AR had higher PP than those with mild (+38 [20-54] mmHg;  $P < .001$ ) and moderate AR (+33 [18-47] mmHg;  $P < .001$ ). The PP cutoffs to divide AR from MR and controls were 38 mmHg (sensitivity [Sn], 100%; specificity [Sp], 19%) for maximal Sn and 61 mmHg (Sn, 43%; Sp, 100%) for maximal Sp. The PP cutoffs to divide severe AR from mild and moderate AR were 57 mmHg (Sn, 100%; Sp, 70%) for maximal Sn and 77 mmHg (Sn, 75%; Sp, 100%) for maximal Sp.

This study shows that Warmblood horses with AR have increased PP. Clinicians may use PP and the above cutoffs to diagnose and stage AR in horses.

Keywords: horse; blood pressure; valvular insufficiency

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## Diagnostische Bedeutung von nicht-invasiven Pulsdruckmessungen bei Warmblutpferden mit Aortenklappeninsuffizienz

Werte von nichtinvasiven Blut- (NIBP) und Pulsdrücken (PP) von Pferden mit Aorten- (AR) und Mitralklappeninsuffizienz (MR) wurden noch nie publiziert. Diese retrospektive Studie untersucht NIBP und PP von gesunden Pferden und Pferden mit AR und MR. Sie bestimmt PP-Grenzwerte zur AR-Erkennung und Schweregradeinteilung.

Bei 73 Pferden (gesund, 10; AR, 31; MR, 32) wurden Echokardiogramme und NIBP-Messungen durchgeführt. Die Pferde wurden nach AR-Schweregrad gruppiert. Der PP wurde zwischen Gruppen verglichen und mit Grenzwertoptimierungskurven wurden PP-Grenzen bestimmt. Die Pferde mit AR zeigten höhere PP-Werte als die Pferde mit MR (mittlere Differenz [95% Konfidenzintervall], +17 [9-26] mmHg,  $P < .001$ ) und gesunde Pferde (+17 [5-30] mmHg;  $P = .004$ ). Die hochgradige AR-Gruppe hatten höhere PP Werte als die leicht- (+38 [20-54] mmHg;  $P < .001$ ) und mittelgradigen AR-Gruppen (+33 [18-47] mmHg;  $P < .001$ ). Die PP-Grenzwerte zur Differenzierung AR von MR und gesunden Pferden waren 38 mmHg (Sensitivität [Sn], 100%; Spezifität [Sp], 19%) mit max. Sn und 61 mmHg (Sn, 43%; Sp, 100%) mit max. Sp. Die PP-Grenzwerte zur Trennung hochgradiger AR von leicht- bis mittelgradiger AR waren 57 mmHg (Sn, 100%; Sp, 70%) mit max. Sn und 77 mmHg (Sn, 75%; Sp, 100%) mit max. Sp.

Die Studie zeigt, dass Warmblutpferde mit AR erhöhte PP haben. Die genannten PP-Grenzwerte können Klinikern Diagnose und Schweregradeinteilung von Pferden mit AR erleichtern.

Schlüsselwörter: Pferd; Blutdruck; Aortenklappeninsuffizienz

# Diagnostic value of noninvasive pulse pressure measurements in Warmblood horses with aortic regurgitation

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## Abstract

**Background:** Noninvasive blood pressures (NIBP) and pulse pressures (PP) have not been published in horses with aortic and mitral regurgitation (AR or MR).

**Objectives:** To investigate NIBP and PP in healthy Warmblood horses and horses with AR and MR and propose PP cutoffs to identify and stage AR severity.

**Animals:** Seventy-three Warmblood horses (healthy, 10; AR, 31; MR, 32).

**Methods:** Retrospective study. All horses had NIBP and an echocardiogram recorded. Cases were categorized based on severity of regurgitation. Pulse pressures were compared among healthy, MR, and AR groups and among AR severity groups. Cutoffs were determined by receiver operating characteristic curve analyses.

**Results:** Horses with AR had higher PP than horses with MR (mean difference [95% confidence interval (CI)], +17 [9-26] mm Hg,  $P < .001$ ) and controls (+17 [5-30] mm Hg;  $P = .004$ ). Horses with severe AR had higher PP compared those with mild (+38 [20-54] mm Hg;  $P < 0.001$ ) and moderate AR (+33 [18-47] mm Hg;  $P < .001$ ). The PP cutoffs to distinguish AR from MR and controls were 38 mm Hg (sensitivity [Sn], 100%; specificity [Sp], 19%) for maximal Sn and 61 mm Hg (Sn, 43%; Sp, 100%) for maximal Sp. The PP cutoffs to distinguish severe AR from mild and moderate AR were 57 mm Hg (Sn, 100%; Sp, 70%) for maximal Sn and 77 mm Hg (Sn, 75%; Sp, 100%) for maximal Sp.

**Conclusions and Clinical Importance:** Horses with AR have increased PP. Noninvasive PP measurements interpreted with provided cutoffs may aid clinicians in diagnosing and staging severity of AR in horses.

KE YWOR DS

blood pressure, hyperkinetic pulse, valvular insufficiency

Abbreviations: ANOVA, analysis of variance; AR, aortic regurgitation; BWT, body weight; DAP, diastolic arterial pressure; EF, left ventricular ejection fraction; FS, left ventricular fractional shortening; HR, heart rate; LA, left atrial; LAD<sub>max</sub>, maximum left atrial diameter at end systole; LAD<sub>max</sub>/LVID<sub>d</sub>, ratio of maximum left atrial diameter to left ventricular internal diameter at end diastole; LV, left ventricle; LVID<sub>d</sub>, left ventricular internal diameter at end diastole; LVIV<sub>d</sub>, left ventricular internal volume at end diastole; MAP, mean arterial pressure; MR, mitral regurgitation; MWT<sub>d</sub>, left ventricular mean wall thickness at end diastole; NIBP, noninvasive blood pressure; PP, pulse pressure; ROC, receiver operating characteristic curve; RWT<sub>d</sub>, left ventricular relative wall thickness at end diastole; SAP, systolic arterial pressure; Sn, sensitivity; Sp, specificity; SV, left ventricular stroke volume.

## 1 | INTRODUCTION

Aortic regurgitation (AR) is a common cardiac disease in horses,<sup>1-3</sup> frequently reported in horses older than 10 years.<sup>3</sup> Resulting in a decrescendo diastolic (often musical) heart murmur, AR is easily diagnosed by careful auscultation. Although a typical diastolic murmur indicates the presence of AR, the murmur alone cannot provide a

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definitive diagnosis or assessment of AR severity and hemodynamic compensation.<sup>4,5</sup> With an AR murmur typically being an incidental finding on clinical examination, the presence of other clinical signs such as exercise intolerance can vary and often even horses with moderate to severe disease do not show any other outward clinical signs.<sup>2,6</sup>

It is important to assess the severity and hemodynamic relevance of AR, because left ventricular (LV) enlargement is considered a prognostic indicator for disease progression and a risk factor for the development of malignant ventricular arrhythmia and sudden cardiac death.<sup>2</sup> Currently, echocardiography is the recommended method for objectively estimating the clinical relevance of a heart murmur.<sup>5,7,8</sup> Thereby, the presence of AR is confirmed and its severity commonly evaluated using the size of the regurgitant jet flow across the aortic valve into the LV.<sup>9</sup> This assessment does not take LV size or shape into consideration, both of which are important for assessing the disease severity. A recent study proposed additional severity scoring criteria, including LV diameter and subjective LV appearance.<sup>10</sup> This combined subjective and objective assessment of LV size, shape, and regurgitant jet size is currently the recommended approach for assessing the AR severity. However, echocardiography requires specialized equipment and a high level of training and operator experience to be accurate and reliable.

There is a need for a stall-side, objective measure of the hemodynamic changes in horses with AR to aid in diagnosis and risk assessment, and to monitor for progression of disease.

In hemodynamically relevant AR, there is both a decrease in diastolic arterial pressure (DAP) as a result of diastolic run-off of blood from the aorta into the LV through the insufficient valve and an increase in systolic arterial pressure (SAP) as a result of increased preload and activation of cardiac compensatory mechanisms (eg, the Frank-Starling mechanism).<sup>11–13</sup> The difference between SAP and DAP is known as pulse pressure (PP). Clinically, this increased amplitude of PP can be appreciated by palpation of a hyperkinetic (referred to as hyperdynamic or a “water-hammer”) pulse. This finding has been described as a subjective clinical marker of hemodynamically relevant AR in horses.<sup>14–16</sup>

Noninvasive blood pressure (NIBP) measurement using a tail cuff placed over the coccygeal artery is becoming easier to perform in the field setting<sup>17</sup> with the availability of portable measurement units, providing an objective measurement of PP (as opposed to subjective palpation of arterial pulse strength). In addition, NIBP measurement requires less training and experience to perform when compared with echocardiography, allowing field clinicians to more easily assess and monitor disease progression. Increased PP has been shown to be a feature of human patients with AR<sup>18</sup> and other cardiovascular diseases.<sup>19–22</sup> One (non-peer-reviewed) study found increased PP in horses with AR with progression of disease,<sup>15</sup> but no data using PP to identify the presence or discriminate the severity of AR have been published to date.

The purpose of our study was to (1) measure NIBP, including PP, in horses with AR and mitral regurgitation (MR) and compare these results with those in healthy controls, (2) provide PP cutoffs that aid in distinguishing horses with AR from horses with MR and healthy controls, and (3) establish PP cutoffs that aid in distinguishing severe

cases of AR from mild and moderate cases. The hypotheses were that horses with AR would have higher PP than horses with MR and control horses, and that horses with severe AR would have higher PP than horses with mild or moderate disease.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population and case selection

This retrospective study included horses that underwent standardized echocardiographic examination at the University of Zurich Equine Hospital between April 2013 and July 2017. Enrollment criteria included a primary diagnosis of AR or MR with echocardiographic severity of mild to severe (based on the size of the regurgitant jet), age >2 years, Warmblood breed, complete physical examination performed, complete echocardiographic examination of good quality (including 2-dimensional, motion mode, and Doppler methods) performed by an experienced operator (Colin C. Schwarzwald or Katharyn J. Mitchell), and 5 NIBP measurements obtained using an NIBP monitor with simultaneously recorded ECG. Control horses had to fulfill the same criteria concerning weight, age, breed, and examinations performed but did not suffer from cardiovascular disease and had no or clinically irrelevant valve regurgitation on echocardiography. Horses were excluded from the study if diagnosed with atrial fibrillation or signs of heart failure, if the primary valvular insufficiency could not be clearly identified, or if they had been sedated before the NIBP recordings were obtained. For horses with multiple examinations, only the first examination of each horse performed during the time period was included.

All examinations were performed according to institutional ethical standards. All owners of clinical patients consented to the examinations as part of the diagnostic evaluation of the presenting problem.

### 2.2 | Noninvasive blood pressure measurements

The NIBP measurements were recorded using an oscillometric method (Medtronic LIFEPAK 15 monitor/defibrillator; Physio-Control, Inc, Redmond, Washington). All horses included in the study were unsedated at the time of blood pressure measurement, and the observer was unaware of the echocardiographic findings and clinical disease severity assessment. An inflatable cuff (Tuff Cuff; CAS medical systems, Inc, Branford, Connecticut) was applied securely to the base of the horse's tail with the bladder of the cuff lying on the coccygeal artery on the underside of the tail head. The cuff size was selected according to the circumference of the base of the tail (cuff width: tail circumference, 0.4–0.6). Once the horse was in a relaxed state, at least 5 NIBP measurements were recorded. Values were not corrected for tail height above heart base. For each recording, the variables SAP, DAP, mean arterial pressure (MAP), and heart rate (HR) were documented and PP was calculated as  $PP = SAP - DAP$ . Measurements with clearly invalid results such as inappropriate HR when compared to auscultation HR or pressure far outside the physiologically expected range (ie,  $SAP >200$  mm Hg,  $DAP <20$  mm Hg) or if the horse was moving excessively were excluded, and the measurement was repeated until 5 valid measurements had been

obtained.<sup>23</sup> For each variable, the average of the 5 recordings of each horse was determined and used for further analyses.

## 2.3 | Echocardiography

Transthoracic echocardiographic examinations and measurements were performed by 2 experienced operators (Colin C. Schwarzwald or Katharyn J. Mitchell) according to a standardized protocol.<sup>24–26</sup> All horses were restrained by an experienced handler, and examinations were performed when the horse was standing quietly with a HR <50 bpm. A high-end echocardiograph (GE Vivid 7 Ultrasound system; GE Healthcare, Glattbrugg, Switzerland) with a phased array transducer (M4S phased array transducer; GE Healthcare) operated at a frequency of 1.7/3.6 MHz (octave harmonics) was used. A single-lead base-apex ECG was recorded simultaneously for timing purposes. Recordings were stored as cine-loops in digital raw data format for subsequent offline analysis (EchoPAC; GE Healthcare). Three representative nonconsecutive cardiac cycles were measured and averaged for each variable. Cycles immediately following a sinus pause, second-degree atrioventricular block, or ectopic beat were excluded from analysis. The HR of each measured cycle was calculated based on the RR interval (in milliseconds) preceding the analyzed cycle ( $HR = 60\,000/RR$ ). All measurements were performed offline at the time of examination of the horses, adhering to a pre-determined measurement protocol that was used throughout data collection. The following variables were measured or calculated for the AR and control group: pulmonary artery diameter at end diastole; aortic sinus diameter at end diastole; maximum left atrial (LA) area and maximum LA diameter ( $LAD_{max}$ ) at end systole, before mitral valve opening; LV internal volume at end diastole ( $LVIV_d$ ); LV ejection fraction (EF); LV stroke volume (SV); LV internal diameter at end diastole ( $LVID_d$ ); LV fractional shortening (FS); LV relative wall thickness at end diastole ( $RWT_d$ ); LV mean wall thickness at end diastole ( $MWT_d$ ); and the ratio of maximum LA diameter to LV internal diameter at end diastole ( $LAD_{max}/LVID_d$ ). Where appropriate, allometric scaling was performed as previously described to correct for differences in body mass.<sup>27</sup> Specifically, LA and LV dimensions were normalized to a body weight (BWT) of 500 kg using the following equations:  $diameter_{[500]} = \text{measured diameter}/BWT^{1/3} \times 500^{1/3}$ ;  $area_{(500)} = \text{measured area}/BWT^{2/3} \times 500^{2/3}$ ;  $volume_{(500)} = \text{measured volume}/BWT \times 500$ . Abnormalities detected on the valve leaflets, extent of cardiac chamber enlargement, severity of the resultant volume overload, size of the regurgitant jet, and relative relationship of jet size to chamber size were judged by the operators. Echocardiographic data from the MR group were not reported because they were not the focus of the study.

## 2.4 | Population grouping and AR severity scoring

Based on auscultation and echocardiographic diagnosis, the cases were separated into groups “AR,” “MR,” and “Control,” and any other diagnoses were excluded. Horses in the control group were clinically healthy and free of cardiac disease based on history, physical examination, and

transthoracic echocardiography. Horses in the AR group were further sorted according to the severity of regurgitation (mild, moderate, or severe), as judged by a scoring method that included subjective criteria (regurgitant jet size, LV size, and apex shape) as well as objective criteria ( $LVIV_{d(500)}$ ). The scoring system was modified from that previously described<sup>10</sup> in that LV volume rather than diameter was evaluated according to current hospital echocardiography standards (see Supplementary Table S1). Three clinicians (Julia Boegli, Colin C. Schwarzwald, Katharyn J. Mitchell), blinded to the previous clinical assessment of the horse, scored each horse, and the average of the 3 scores was used to sort the horses into 3 groups. Age, sex, breed, BWT, reason for presentation, primary and secondary diagnosis and corresponding severities, NIBP measurements, HR, and subjective pulse quality obtained by digital palpation (moderate, strong, or hyperkinetic) were reported for each case.

## 2.5 | Data analysis and statistical methods

Data collection, graphical presentation, data analysis, and statistics were performed using commercially available computer software (Microsoft Excel; Microsoft, Redmond, Washington; GraphPad Prism version 7.03; GraphPad Software, Inc, San Diego, California; Sigmaplot version 12.3 for Windows; Systat Software GmbH, Erkrath, Germany).

Distribution and spread of the data were evaluated visually using raw data with dot plots and box-and-whisker plots. Normally distributed data were reported as mean  $\pm$  SD, whereas variables that were not normally distributed were reported as median (minimum-maximum). The level of significance for all statistical analyses was  $P < .05$ .

A chi-squared test was used to compare the distribution of sex among the control, AR, and MR groups. A Fisher's exact test was used to compare subjective (palpation) assessment of pulse quality (hyperkinetic versus moderate or strong) with the echocardiographic severity score assessment (severe versus mild or moderate). Sensitivity (Sn) and specificity (Sp) were calculated from the contingency table using the Wilson-Brown method.<sup>28</sup>

Age, BWT, HR, SAP, DAP, MAP, and PP were compared among the AR, MR, and control groups, and among the different AR severity groups, respectively, using 1-way analysis of variance (ANOVA) and Tukey's multiple comparisons post hoc test. Echocardiographic data from the different AR severity groups and the control group also were compared using 1-way ANOVA and Tukey's multiple comparisons post hoc test. To investigate the influence of HR on PP measurements, a multiple linear regression analysis was performed, with PP as the dependent variable and HR and AR severity (reference-coded as dummy variable) as independent variables. Normal distribution and homoscedasticity of the residuals were confirmed by assessment of a histogram, normal probability plot, and a scatterplot of the residuals.

Receiver operating characteristic curve (ROC) analysis was used to determine PP cutoffs to distinguish AR cases from MR and control groups and to distinguish horses with severe AR from those with mild to moderate AR, respectively. Two separate cutoffs, including the cutoff to maximize Sn and the cutoff to maximize Sp, were determined for each ROC analysis. Additionally, the cutoff resulting in the highest



Youden's index ( $Sp + Sn - 1$ ), maximizing both the combined  $Sn$  and  $Sp$ , was determined.<sup>29</sup> The area under the curve,  $Sn$ , and  $Sp$  were reported with their 95% confidence intervals. In addition, the positive and the negative likelihood ratios were reported for each cutoff.

### 3 | RESULTS

#### 3.1 | Study population and case selection

Ten control horses, 32 horses with MR, and 31 horses with AR were identified in the medical records as meeting the inclusion criteria for the study. Specific information on the study population can be found in Tables 1 and 2.

Reasons for presentation were investigation of heart murmurs heard incidentally on physical examination (AR, 18 horses; MR, 23 horses; control, 2 horses) or for follow-up examinations (AR, 9 horses; MR, 5 horses; control, 1 horse), weakness or collapsing episodes (AR, 2 horses; MR, 2 horses; control, 1 horse), cough (AR, 1 horse), arrhythmia (MR, 1 horse; control, 3 horses), decreased performance (MR, 1 horse; control, 3 horses), and trauma (AR, 1 horse). The 10 control horses were considered cardiovascularly normal (6 horses) or had clinically irrelevant (trace or trivial) valve regurgitation (4 horses). The 3 horses presented for evaluation of arrhythmia had physiological sinus arrhythmia and 2nd-degree atrioventricular block at rest. Horses with decreased performance or collapse were diagnosed with problems of other organ systems (left recurrent laryngeal neuropathy, asthma, orthopedic disease).

The mean age of horses with AR was significantly higher when compared to the MR and control group (Table 1), whereas BWT or sex did not differ significantly among the 3 groups. Within the AR group, the horses in the mild group were significantly younger than the horses in the severe group (Table 2), but no difference in BWT was identified.

TABLE 1 Population characteristics of the main disease groups

	Main disease groups			F-test <i>P</i> value
	Control	MR	AR	
n	10	32	31	
Age (years)	10 ± 5 <sup>a</sup>	11 ± 5 <sup>a</sup>	17 ± 5 <sup>b</sup>	<.001
Sex				
Female	4	8	8	.63
Male	6	24	23	
Body weight (kg)	595 ± 33	576 ± 50	584 ± 51	.58
Pulse quality				
Moderate	1	3	2	nt
Strong	9	29	23	nt
Hyperkinetic	0	0	6	nt

Numerical values are reported as mean ± SD. Significance was set at  $P < .05$ . Different-letter superscripts are indicative of a significant difference, whereas the same-letter superscripts indicates there is no difference among the groups.

Abbreviations: AR, aortic regurgitation; MR, mitral regurgitation; n, number of horses; nt, not tested.

#### 3.2 | Echocardiography of AR horses

The severity scoring system classified 8 horses with severe AR, 15 horses with moderate AR, and 8 horses with mild AR. Concurrent MR was observed and considered trivial (2 horses), trivial to mild (6 horses), mild (3 horses), or mild to moderate (3 horses) in horses with AR as the primary valvular regurgitation. The echocardiographic data are found in Table 2. Horses with severe AR had increased LA diameter and area compared to control horses or horses with mild AR. The LV size (LVID<sub>d</sub>, LVIV<sub>d</sub>) was significantly larger, and RWT<sub>d</sub> and LAD<sub>max</sub>/LVID<sub>d</sub> were significantly lower in horses with severe AR compared to all other groups. Horses with mild AR had significantly increased MWT<sub>d</sub>. Although the indices of LV systolic function (EF and FS) were not different among AR severity subgroups and control horses, the SV of horses with severe AR was significantly increased compared to horses with mild and moderate AR, as well as compared to control horses.

#### 3.3 | Noninvasive blood pressure measurements

Table 3 and Figures 1 and 2 compare the NIBP data among the 3 disease groups and within the AR severity subgroups. The AR group had increased SAP compared to the MR group and increased PP compared to the MR and control groups, whereas MAP and DAP were not different among the groups. Within the AR severity subgroups, horses with severe AR had significantly decreased DAP and significantly increased PP compared to horses with mild AR, but no significant differences in SAP, MAP, or HR were found. Compared to horses with moderate AR, horses with severe AR had significantly increased SAP and significantly increased PP, but no significant differences in DAP, MAP, or HR were found.

No significant effect of HR on PP was identified in the multiple regression model ( $P = .4$ ).

Results of the ROC analysis reporting the different cutoffs to distinguish AR from MR and control horses and to detect horses with severe versus mild and moderate AR are found in Table 4 and Figures 1 and 2.

When subjective pulse quality (moderate or strong versus hyperkinetic) was compared to the echocardiographic severity score (mild or moderate versus severe), palpation of a hyperkinetic pulse was significantly associated with severe AR (Fisher's exact test,  $P = .03$ ). However, palpation of a hyperkinetic pulse did not perform as well as NIBP measurement of PP for predicting severe AR ( $Sn$ , 50%;  $Sp$ , 91%; positive likelihood ratio, 5.8). Figure 3 shows the PP measurements in horses with a moderate and strong versus hyperkinetic pulse quality on palpation.

### 4 | DISCUSSION

In our study, NIBP values were compared among horses with AR and MR, and control horses to determine NIBP values that best indicate the presence and severity of AR. The results indicate that PP can be

TABLE 2 Population and echocardiographic characteristics of each AR severity subgroup and the control group

	AR groups				F-test p value
	Mild	Moderate	Severe	Control	
n	8	15	8	10	
Age (years)	14 ± 6 <sup>a,c</sup>	17 ± 3 <sup>a,b</sup>	20 ± 5 <sup>b</sup>	10 ± 5 <sup>c</sup>	.045
Sex					
Female	4	4	0	4	nt
Male	4	11	8	6	
Body weight (kg)	588 ± 69	587 ± 44	573 ± 48	595 ± 33	.807
Pulse quality					
Moderate	1	1	0	1	nt
Strong	7	12	4	9	nt
Hyperkinetic	0	2	4	0	nt
AR severity score	5 (4-5)	7 (6-9)	11 (10-13)		nt
Echocardiographic dimensions					
PAD <sub>ed</sub> (cm)	6.8 ± 0.6 <sup>a</sup>	7.2 ± 0.5 <sup>a</sup>	7.5 ± 0.8 <sup>a</sup>	6.8 ± 0.6 <sup>a</sup>	.034
AoD <sub>ed</sub> (cm)	8.4 ± 0.8	8.3 ± 0.8	8.2 ± 0.4	7.8 ± 0.7	.19
LAA <sub>max</sub> (500) (cm <sup>2</sup> )	90 ± 14 <sup>a</sup>	97 ± 11 <sup>a,b</sup>	107 ± 12 <sup>b</sup>	87 ± 8 <sup>a</sup>	.002
LAD <sub>max</sub> (500) (cm)	11.7 ± 1.1 <sup>a,c</sup>	12.3 ± 0.7 <sup>a,b</sup>	13.2 ± 0.8 <sup>b</sup>	11.2 ± 0.7 <sup>c</sup>	<.001
LVID <sub>d</sub> (500) (cm)	11.1 ± 0.5 <sup>a</sup>	12.4 ± 1.2 <sup>b</sup>	15.1 ± 1.3 <sup>c</sup>	10.8 ± 0.6 <sup>a</sup>	<.001
LVIV <sub>d</sub> (500) (mL)	1078 ± 165 <sup>a,c</sup>	1309 ± 204 <sup>a,c</sup>	2067 ± 451 <sup>b</sup>	1043 ± 137 <sup>c</sup>	<.001
RWT <sub>d</sub>	0.59 ± 0.07 <sup>a</sup>	0.47 ± 0.06 <sup>b</sup>	0.38 ± 0.06 <sup>c</sup>	0.53 ± 0.07 <sup>a,b</sup>	<.001
MWT <sub>d</sub> (cm)	3.4 ± 0.4 <sup>a</sup>	3.0 ± 0.2 <sup>b</sup>	3.0 ± 0.3 <sup>b</sup>	3.0 ± 0.3 <sup>b</sup>	.005
LAD <sub>max</sub> /LVID <sub>d</sub>	1.1 ± 0.1 <sup>a</sup>	1.0 ± 0.1 <sup>a</sup>	0.9 ± 0.1 <sup>b</sup>	1.0 ± 0.1 <sup>a</sup>	.001
FS (%)	42 ± 8	39 ± 7	40 ± 4	45 ± 4	.18
EF (%)	71 ± 4	73 ± 4	73 ± 4	75 ± 4	.12
SV (mL)	888 ± 144 <sup>a,c</sup>	1120 ± 211 <sup>a,c</sup>	1754 ± 516 <sup>b</sup>	931 ± 119 <sup>c</sup>	<.001
HR (bpm)	39 ± 10	36 ± 7	38 ± 5	39 ± 5	.59

Numerical values are reported as mean ± SD or median (range). Severity score is based on a modified scoring method, see Supplementary Table S1. Significance was set at  $P < .05$ . Different-letter superscripts are indicative of a significant difference, whereas the same-letter superscript indicates there is no difference between groups.

Abbreviations: AoD<sub>ed</sub>, aortic sinus diameter at end diastole; AR, aortic regurgitation; EF, ejection fraction; FS, fractional shortening; HR, heart rate; LAA<sub>max</sub> (500), maximum left atrial area, allometrically scaled to 500 kg; LAD/LVID<sub>d</sub>, ratio of maximum left atrial diameter to left ventricular internal diameter at end diastole; LAD<sub>max</sub> (500), maximum left atrial diameter, allometrically scaled to 500 kg; LVID<sub>d</sub> (500), left ventricular internal diameter at end diastole, allometrically scaled to 500 kg; LVIV<sub>d</sub> (500), left ventricular internal volume at end diastole, allometrically scaled to 500 kg; MWT<sub>d</sub>, mean wall thickness at end diastole; n, number of horses; PAD<sub>ed</sub>, pulmonary artery diameter at end diastole; RWT<sub>d</sub>, relative wall thickness at end diastole; SV, stroke volume.

used as a diagnostic aid in detection and staging of AR severity in horses.

#### 4.1 | Noninvasive blood pressures

The mean SAP, DAP, MAP, and HR recorded for the MR and control groups in our study were similar to the reference values reported in the veterinary medical literature using an ultrasonic blood flow detector technique and an oscillometric method.<sup>30,31</sup> Although PP of healthy horses is only specifically reported in a single paper,<sup>30</sup> reference values for PP can be deduced from other reported SAP and DAP values obtained in healthy horses and were similar to those found in our control horses.<sup>31</sup> Correction for tail height above heart base is necessary to evaluate the accuracy of NIBP measurements of SAP, DAP, and MAP

among different sized horses but is redundant when assessing changes in PP, because both SAP and DAP will change by the same magnitude in a given horse. Although the tail height above heart base was not recorded in our study, an attempt to standardize the population of horses was made by including only horses of Warmblood breed older than 2 years. Body weight did not differ among the groups of horses, making it more likely that the horses included in our study were of a similar stature.

#### 4.2 | NIBP differences in AR, MR, and control horses

Pulse pressure was significantly increased in horses with AR compared to horses with MR and healthy controls. Similar results have been found in human medicine, and widened PP can be a diagnostic aid for

TABLE 3 (A) Noninvasive blood pressure values of all horses in each group<sup>a</sup>; (B) F-test and post hoc *P*-values of the comparison in one-way ANOVA

(A)	Main groups comparison			AR groups comparison		
	Control (n = 10)	MR (n = 32)	AR (n = 31)	Mild (n = 8)	Moderate (n = 15)	Severe (n = 8)
HR (bpm)	38 ± 4	39 ± 7	39 ± 6	36 ± 7	41 ± 14	40 ± 2
SAP (mm Hg)	116 ± 10	118 ± 12	127 ± 18	126 ± 17	120 ± 15	142 ± 15
MAP (mm Hg)	88 ± 9	88 ± 11	85 ± 14	93 ± 14	83 ± 13	80 ± 15
DAP (mm Hg)	71 ± 9	73 ± 11	65 ± 15	76 ± 11	65 ± 12	55 ± 17
PP (mm Hg)	45 ± 8	45 ± 7	62 ± 20	50 ± 8	55 ± 11	88 ± 21
(B)	Main groups comparison		AR groups comparison			
	F-Test <i>P</i> -value	Tukey's multiple comparisons post hoc <i>P</i> -value	F-Test <i>P</i> -value	Tukey's multiple comparisons post hoc <i>P</i> -value		
HR (bpm)	.88		.53			
SAP (mm Hg)	.02	C versus MR = .94; C versus AR = .09; MR versus AR = .03	.009	Mi versus Mo = .61; Mi versus S = .11; Mo versus S = .007		
MAP (mm Hg)	.19		.13			
DAP (mm Hg)	.05		.02	Mi versus Mo = .16; Mi versus S = .011; Mo versus S = .23		
PP (mm Hg)	<.001	C versus MR = .99; C versus AR = .004; MR versus AR <.001	<.001	Mi versus Mo = .72; Mi versus S <.001; Mo versus S <.001		

Significant differences between groups are highlighted in *italics*.

Abbreviations: ANOVA, analysis of variance; AR, aortic regurgitation; C, control; DAP, diastolic arterial pressure; MAP, mean arterial pressure; Mi, mild aortic regurgitation; Mo, moderate aortic regurgitation; MR, mitral regurgitation; PP, pulse pressure; S, severe aortic regurgitation; SAP, systolic arterial pressure.

<sup>a</sup>A one-way ANOVA with Tukey's multiple comparison post hoc test was performed. Level of significance was set at *P* < .05. Values are reported as mean ± SD.

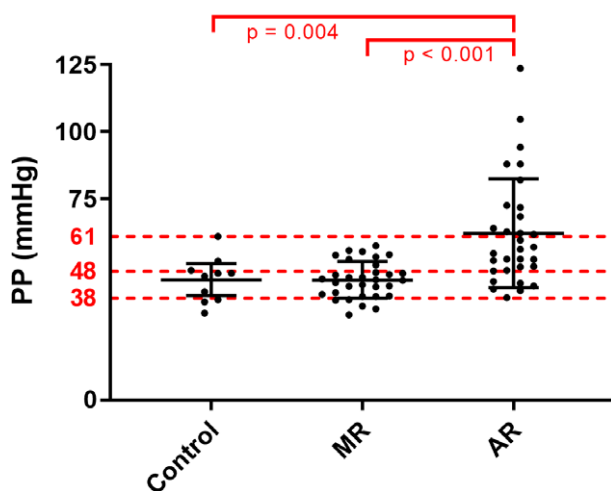


FIGURE 1 Dot plot showing pulse pressure measurements from control horses compared with horses diagnosed with mitral (MR) or aortic (AR) regurgitation. The mean and SD for each group is displayed. The red dotted lines represent the receiver operating characteristic curve analysis cutoffs of highest sensitivity (38 mm Hg), highest specificity (61 mm Hg), and the Youden index-based cutoff (48 mm Hg). Significant differences were detected with a 1-way analysis of variance, between control horses and horses with AR (*P* = .004) and between horses with AR and MR (*P* < .001).

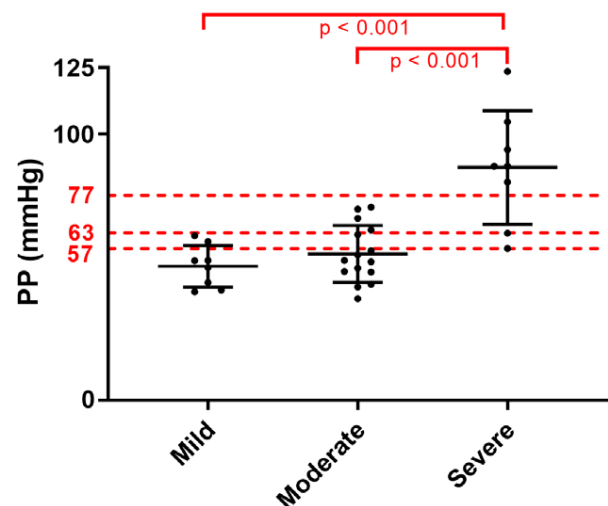


FIGURE 2 Dot plot showing pulse pressure measurements from horses with mild, moderate and severe aortic regurgitation (AR). The mean and SD for each group is displayed. The red dotted lines represent the receiver operating characteristic curve analysis cutoffs of highest sensitivity (57 mm Hg), highest specificity (77 mm Hg), and the Youden index-based cutoff (63 mm Hg). Significant differences were detected with a 1-way analysis of variance, between horses with mild and severe AR (*P* < .001) and between horses with moderate and severe AR (*P* < .001).

TABLE 4 Receiver operating characteristic curve analyses

	AUC (95% CI)	PP cutoff (mm Hg)	Sn (%) (95% CI)	Sp (%) (95% CI)	Positive LR	Negative LR
AR versus MR and control	0.83 (0.74-0.93)					
High Sn		38	100 (88-100)	19 (8-33)	1.2	0
Youden Index		48	83 (65-94)	74 (59-87)	3.3	0.23
High Sp		61	43 (26-63)	100 (92-100)	∞	0.57
Severe versus mild and moderate AR	0.94 (0.85-1.00)					
High Sn		57	100 (63-100)	70 (47-87)	3.3	0
Youden Index		63	88 (47-100)	83 (61-95)	5	0.15
High Sp		77	75 (35-97)	100 (85-100)	∞	0.25

Pulse pressure cutoff values and respective sensitivities, specificities, and likelihood ratios to diagnose AR versus MR and control horses and severe AR versus mild and moderate AR, respectively.

Abbreviations: AR, aortic regurgitation; AUC, area under curve; CI, confidence interval; LR, likelihood ratio; MR, mitral regurgitation; PP, pulse pressure; Sn, sensitivity; Sp, specificity.

identifying people with AR.<sup>12</sup> In a study on experimental AR in anesthetized dogs, PP increased from  $23 \pm 4$  mm Hg before AR induction to  $61 \pm 22$  mm Hg after AR induction.<sup>32</sup> In another study, anesthetized dogs with experimentally induced AR experienced an immediate widening of PP once regurgitation occurred.<sup>13</sup> Physiologically, this can be explained by considering the cardiovascular changes that AR causes. In AR, the diastolic runoff of regurgitant blood flow from the aorta back into the LV causes a decrease in DAP. When the regurgitant volume is hemodynamically relevant, it adds substantially to ventricular preload, activating the Frank-Starling mechanism and increasing stroke volume. The increased volume of blood ejected into the aorta then results in a steady or even increased SAP. Clinically, individuals with severe AR often have hyperkinetic or “water hammer” pulses,<sup>11,12,16,33,34</sup> which can be felt as a bounding pulse when palpating a peripheral artery.

In our study, the widened amplitude between SAP and DAP is illustrated by the higher PP in horses with AR compared to control horses and horses with MR, and in horses with increasing severity of AR. In this group of horses with AR, there was no apparent effect of HR on PP. This is an interesting finding, because horses with lower HR would have longer periods of diastole and larger regurgitant volumes entering the LV, theoretically resulting in lower DAP, whereas the effect should be opposite (increasing DAP) in horses with higher HR. The lack of a wider range in HR in this population of horses prevents this hypothesis from being fully tested.

The significantly increased PP values in Warmblood horses with AR may aid clinicians in the field when confirming AR if echocardiography is

unavailable, when determining whether a horse with AR should be referred for further evaluation or when assessing whether the disease has progressed in severity. Invasive blood pressure monitoring is uncommonly performed in field practice, but NIBP monitoring presents a tool that could be implemented easily in the field setting.<sup>31,35-41</sup>

The provided PP cutoffs (Table 4) can be implemented in clinical situations, depending on whether a high Sn or high Sp is required for

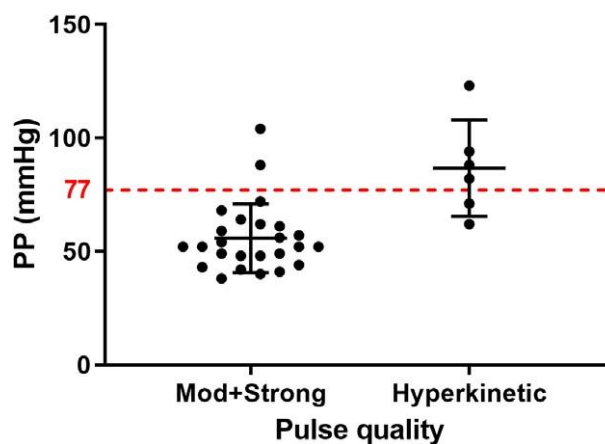


FIGURE 3 Dot plot showing the corresponding pulse quality (moderate and strong, hyperkinetic) versus pulse pressure measurements from horses with AR. The mean and SD for each group is displayed. The red dotted line represents the receiver operating characteristic curve cutoff with the highest specificity (77 mm Hg)

disease classification. If the aim is to rule out a horse having AR, a PP < 38 mm Hg indicates a horse is unlikely to have AR, whereas a PP > 61 mm Hg is highly indicative of AR. Pulse pressures ranging between 38 and 61 mm Hg represent an equivocal zone, and the Youden index-based cutoff of 48 mm Hg may lack sufficient diagnostic accuracy to be clinically useful. The PP cutoffs to determine the severity of AR function in the same way. Obtaining results above the cutoff of 77 mm Hg will identify most horses with severe AR. Results below the cutoff of 57 mm Hg will identify horses that most likely do not have severe AR. Again, the PP range of 57–77 mm Hg represents an equivocal zone, containing the Youden index-based cutoff of 63 mm Hg. These cutoffs may assist clinicians when judging the hemodynamic relevance of AR in an individual horse in combination with auscultation and other physical examination findings.

Monitoring the progression of AR is important because horses with hemodynamically relevant AR are anecdotally reported to be at an increased risk of collapse and sudden cardiac death.<sup>2</sup> Hence, independent of the respective cutoffs, monitoring PP over time might aid in detecting clinically relevant progression of AR in individual horses. In our study, NIBP and echocardiographic evaluation only were performed at a single time point. Further studies will be required to see how PP trends change in the same horse over time if AR severity progresses and to determine the magnitude of increase in PP that would suggest clinically relevant progression of disease. It is also conceivable that if AR progresses to the point of myocardial failure, PP could theoretically decrease, particularly if systemic and LV pressures equalize in a hemodynamically unstable patient. Longer term monitoring of PP in AR patients would give valuable insight into the pathophysiology and hemodynamic changes associated with progression of AR.

Comparison between subjective assessment of peripheral pulses by digital palpation and objective PP assessment utilizing NIBP measurements showed that although palpation of a hyperkinetic pulse is strongly indicative of severe AR, not all horses with severe AR will have this clinical finding. This observation may be related partly to the body condition score of the horse as well as individual clinician skill and experience. Therefore, utilizing NIBP measurement of PP improves diagnostic accuracy compared to physical examination alone.

### 4.3 | Echocardiography

Echocardiographic measurements were reported for documentation and description of the different AR severity groups. Because indices of LV size were included in the AR severity scoring system used to classify AR severity, it is logical that these indices would be different among the AR severity subgroups. The extent of LV enlargement in the AR severity subgroups was similar to that recently reported in other studies assessing the severity of AR using echocardiographic measurements.<sup>10,42,43</sup> However, it is also clear that horses with severe AR show signs of LA enlargement indicating the hemodynamic relevance of severe AR resulting in increased preload of both the LV and LA. The finding of increased MWT<sub>d</sub> and RWT<sub>d</sub> in horses with mild AR indicates that some concentric remodeling occurs in this population of horses, whereas the decreased RWT<sub>d</sub> seen in the horses with severe

AR indicates that the chamber enlargement is becoming disproportionate to wall thickness. The fact that indices of LV systolic function are not different among the AR severity subgroups highlights the difficulty in using these variables to judge the severity of AR, as has been described in 2 recent studies evaluating other methodologies to identify subtle changes in myocardial function.<sup>42,43</sup>

Our study does not assert that NIBP measurements should replace echocardiography in the assessment of horses with AR. Rather, NIBP measurements, and particularly PP measurements, can provide additional information on the hemodynamic relevance of AR to guide practitioners in their assessment of these horses in both field and hospital settings.

## 5 | LIMITATIONS

Because of the nature of case selection in this retrospective study, the size of the control group was small in comparison to the AR and MR groups. This likely caused a lack of statistical power to detect some differences among the groups (eg, differences in DAP among the disease groups). In addition, the control group was a convenience sample that contained horses that were presented to the hospital for evaluation of arrhythmia, murmur, poor performance, or collapse. These horses were found to be cardiovascularly normal, and the NIBP ranges were similar to those reported previously for healthy horses.<sup>30,31</sup>

Additionally, the within-day and between-day variability of PP measurements in both healthy horses and horses with AR was not documented. A recent study (data unpublished) from our laboratory has found that PP measurement in healthy horses has a within-day/within-operator coefficient of variation of 10.3% and a between-day/within-operator coefficient of variation of 8.8%, both of which are considered acceptable amounts of variation. However, we currently do not have any data on the variability of PP measurements in horses with AR, and further research in this area is required.

Another limitation of our study is the possibility of classification bias of disease severity. The AR scoring system implemented both objective and subjective criteria to minimize bias and a similar scoring system previously had been described,<sup>10</sup> but neither of the scoring systems has yet been validated, because of a lack of a reference standard to categorize AR severity in horses. Additionally, in the MR group, the severe category was underrepresented in comparison to the severe category in the AR group (data not shown), because individuals with severe MR often suffer from secondary atrial remodeling and may present with atrial fibrillation.<sup>1,44</sup> The NIBP monitors misreport blood pressure values when a horse is arrhythmic, which was the reason why horses with atrial fibrillation were excluded from our study. The relevance of this underrepresentation is unclear and should be further investigated, but the hemodynamic effects of severe MR are not considered likely to affect PP.

Older horses were overrepresented in the AR group; similar results have been reported in previous studies investigating the epidemiology of AR in horses.<sup>2,3,6</sup> The effect of age (independent of AR) on PP is unknown in horses, although in human patients PP is reported to increase with age, as a result of vascular stiffness leading to increased SAP.<sup>45</sup> A much larger study population with individuals of various ages



would be required to investigate any association between age and PP in horses. This was beyond the scope of our study. In addition, various other cardiovascular diseases can result in a widening of PP in people (including systemic hypertension and atherosclerosis),<sup>20,22</sup> and thus PP always should be interpreted in conjunction with physical examination findings and the presence of a left-sided diastolic murmur. If an increased PP is identified in a horse without appreciable AR, the horse should be evaluated for the presence of other cardiovascular diseases (eg, aortic-cardiac fistula, systemic hypertension).

Lastly, our results are only valid for Warmblood horses and when NIBP is measured using an identical NIBP monitoring device with the appropriate cuffs. Extrapolation to other horse breeds, other monitors, or different cuff types should not be attempted unless appropriate validation studies have been performed.

## 6 | CONCLUSIONS

In conclusion, calculation of PP from NIBP measurements can provide an objective assessment of the hemodynamic consequences of AR in Warmblood horses. Measurement of NIBP in horses is a straightforward procedure that can be performed easily in a field setting. Although NIBP cannot replace echocardiography in diagnosing and staging severity of valvular disease, it can provide additional objective data on the cardiovascular state of a horse suffering from AR, thus aiding the clinician in determining the clinical relevance of a heart murmur. By utilizing the provided cutoffs of PP, clinicians can assess the likelihood of AR being hemodynamically relevant and provide additional information to owners and riders. Further studies will be required to define the clinical value of sequential PP measurements over time to monitor clinically relevant progression of AR.

## ACKNOWLEDGMENT

Preliminary results of this study have been presented as an oral research report at the 2017 ECEIM Forum, Budapest, Hungary, November 4, 2017.

## CONFLICT OF INTEREST DECLARATION

Colin Schwarzwald serves as Associate Editor for the Journal of Veterinary Internal Medicine. He was not involved in review of this manuscript.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Clients consented to all examinations performed on their horses as part of the clinical diagnostic investigation.

## HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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## AR Severity Scoring Sheet

Operator	
Date	

KG Number	
Owner Name	
Horse Name	
Visit Date	

This scoring sheet's purpose is to compare the efficacy of the Zurich Method, the Ghent Method<sup>1</sup> and Color Doppler Method (modified Lesley Young<sup>2</sup>) when determining disease severity in Warmbloods with Aortic Valve Regurgitation (AR). Please evaluate the horse indicated and circle the appropriate point based on the supplied criteria. LVIVd and LVIDd size, point total and severity score will be filled out by JB.

### 1. Color Doppler Diagnosis (modified Lesley Young<sup>2</sup>)

Zurich	
Criteria	Severity
<ul style="list-style-type: none"> <li>• Jet <math>\leq \frac{1}{4}</math> LVOT Area</li> <li>• Jet visible in multiple planes</li> </ul>	Mild
<ul style="list-style-type: none"> <li>• Jet <math>&gt; \frac{1}{4} \leq \frac{3}{4}</math> LVOT Area</li> <li>• Small vena contracta</li> </ul>	Moderate
<ul style="list-style-type: none"> <li>• Jet <math>&gt; \frac{3}{4}</math> LVOT Area</li> <li>• Wide vena contracta</li> </ul>	Severe

### 2. LVIV<sub>d</sub> and LVID<sub>d</sub> size

Zurich	
LVIV <sub>d</sub> [500] S <sup>3</sup>	Points
$\leq 1300$ ml	1
1301 ml – 1800 ml	2
1801 ml – 2300 ml	3
$> 2300$ ml	4

Ghent	
LVID <sub>d</sub> [500]	Points
$< 13$ cm	1
13 – 14 cm	2
$> 14$ cm	3



**3. Jet size:** Please evaluate the size of the regurgitant jet (as visualized by Color Flow Doppler).

Zurich	
Jet size compared to LVOT <sup>2</sup>	Points
< ¼ LVOT Area	1
< ½ LVOT Area	2
≤ ¾ LVOT Area	3
> ¾ LVOT Area	4

Ghent	
Jet size compared to LV	Points
< ⅓ LV Area	1
≤ ⅔ LV Area	2
> ⅔ LV Area	3

**4. Subjective evaluation:** Please evaluate the left ventricle from the four chamber view.

Zurich/Ghent	
Criteria evaluated	Points
<ul style="list-style-type: none"> <li>Normal ventricle, no enlargement</li> <li>Normal apex shape</li> </ul>	1
<ul style="list-style-type: none"> <li>Normal ventricle, mild enlargement</li> <li>Normal apex shape</li> </ul>	2
<ul style="list-style-type: none"> <li>Large ventricle, moderate enlargement</li> <li>round apex shape</li> </ul>	3
<ul style="list-style-type: none"> <li>Large ventricle, moderate enlargement</li> <li>globoid apex shape</li> </ul>	4
<ul style="list-style-type: none"> <li>Large ventricle, severe enlargement</li> <li>Very globoid apex shape</li> </ul>	5

**5. Total score**

Score Zurich: \_\_\_\_\_

Score Ghent: \_\_\_\_\_

Point Score	Severity
3 – 5	Mild
6 – 9	Moderate
10 – 13	Severe

Point Score	Severity
3 – 4	Mild
5 – 7	Moderate
≥ 8	Severe

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1. Ven S, Decloedt A, Van Der Vekens N, et al. Assessing aortic regurgitation severity from 2D, M-mode and pulsed wave Doppler echocardiographic measurements in horses. The Veterinary Journal 2016;210:34-38.
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